EXHIBIT 2

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Sent: Monday, July 05, 1999 3:18 PM
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Embargo: May 5th, 1999 at 10.00 a.m. (Brussels time)

ABOUT LUVOX® TABLETS

LUVOX® Tablets was the first medication approved by the Food and Drug Administration in the USA for Obsessive Compulsive Disorder (OCD) in children and adolescents. LUVOX® Tablets is safe and effective and is the medication most often prescribed by psychiatrists to treat this illness. Psychotropic drugs like LUVOX® Tablets are also prescribed to psychiatric patients, who sometimes show unexpected behavior.

Thousands of children and adolescents who suffer from OCD have been safely and effectively treated for this condition with LUVOX® Tablets. Many physicians, parents and mental health organizations have expressed themselves on the Internet and in the US press (i.e. Washington Post,

N.Y. Times, ABC News) stressing how important, safe and effective LUVOX® medication is.

There is no evidence to suggest a causal relationship between the prescribed use of LUVOX® Tablets and violent or suicidal behavior. As with all medications, LUVOX® Tablets must be used as prescribed. In a statement made on April 28, 1999, Rodrigo Munoz, M.D., President of the American Psychiatric Association, said: "Despite a decade of research, there is little valid evidence to prove a causal relationship between the use of anti-depressant medications and destructive behavior. On the other hand, there is ample evidence that undiagnosed and untreated mental illness exacts a heavy toll on those who suffer from these disorders as well as those around them".

We are aware of the news reports surrounding Eric Harris and the tragedy in Colorado, but have no specific information about his medical history, his doctor's prescription or whether he was taking the medication and, if so, whether he was taking the medication properly.

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See also :
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EXHIBIT 3

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	20,243
Sponsor:	Solvay Pharmaceuticals
Clock Date:	December 30, 1991

Drug Name

Generic Name:	Fluvoxamine Maleate
Proposed Trade Name:	Luvox

Drug Categorization

Pharmacological Category:	Selective Serotonin Reuptake Inhibitor
Proposed Indication:	Obsessive Compulsive Disorder
NDA Classification:	1S
Dosage Forms, Strengths, and Route of Administration:	25mg, 50mg, 100mg, and 150mg film-coated tablets.

Reviewer Information

Clinical Reviewer:	Gregory M. Dubitsky, M.D.
Review Completion Date:	October 22, 1993

2.0 Background

2.1 Indication

The only other drug currently approved by the FDA for treatment of OCD is clomipramine (Anafranil), which was approved in 1990 on the basis of demonstrated moderate effectiveness in treating obsessions and compulsions in patients with moderate to severe DSM-III OCD in controlled clinical trials. It is claimed that fluvoxamine has a side effect profile which is superior to that of clomipramine, most notably a low incidence of anticholinergic side effects, no clinically significant cardiotoxicity and an extremely low seizure rate.

Fluoxetine (Prozac), another selective serotonin reuptake inhibitor which is approved for depression, has also been shown to be helpful in treating some patients with OCD in investigational trials and was recommended for approval for this indication by the Psychopharmacologic Drugs Advisory Committee in July 1993.

Other available drugs, such as tricyclic antidepressants, have not demonstrated consistent efficacy in OCD.

2.2 Related IND's and NDA's

Other selective serotonin reuptake inhibitors currently approved in the U.S. are summarized below.

Trade Name	Generic Name	NDA #	Indication
Prozac	Fluoxetine	18,936	Depression
Zoloft	Sertraline	19,839	Depression
Paxil	Paroxetine	20,031	Depression

IND (sponsored by Lawrence H. Price, M.D. of Yale University) and IND (sponsored by Daniel Winstead, M.D. of Tulane University) are IND's in addition to the sponsor's IND which have been filed for the investigational use of fluvoxamine in the United States and are currently active. Records indicate that 10 other IND's for the investigational use of fluvoxamine have been filed over the past several years; these appear to have been cancelled or withdrawn or are inactive at this time.

2.3 Administrative History

Fluvoxamine maleate is a novel unicyclic compound which was first synthesized in The Netherlands in the early 1970's. It was

discovered to selectively inhibit the reuptake of serotonin into presynaptic neurons both in vitro and in vivo and, given this property, fluvoxamine was investigated with the intention of ultimately seeking marketing approval for the treatment of depression.

IND was submitted to the FDA on October 15, 1975 for the initiation of trials of fluvoxamine in the treatment of depression. Studies commenced and a patent was issued for fluvoxamine maleate on April 18, 1978, to expire in 1995. A pre-NDA meeting convened on May 19, 1983, to discuss required data and the format to be used for the NDA submission.

NDA for the use of fluvoxamine in depression was submitted on December 20, 1983, and included a total of 71 separate studies and 1,172 subjects treated with fluvoxamine over an 8 year period in Europe and North America. After a thorough review of this submission, a not-approvable letter was sent to the sponsor based primarily on failure to adequately demonstrate efficacy. Also, data contained in the Pharmacology, Chemistry, and Biopharmaceutics sections was considered to be deficient. On October 3, 1985, the sponsor informed the FDA of its intent to file an amendment to the NDA but an adequate amendment had not been filed as of October 2?. 1990, and the NDA was considered to be withdrawn.

In the meanwhile, the sponsor elected to pursue studies to demonstrate the efficacy and safety of fluvoxamine for the treatment of obsessive-compulsive disorder based on the theory that CNS serotonergic dysfunction was implicated in the biology of OCD. On September 18, 1987, an amendment to the original IND was filed for the initiation of studies 5529 and 5534, two adequate and well-controlled studies which, together with safety data accumulated over the previous several years, were intended to provide the basis for the eventual approval of fluvoxamine for OCD.

Given the vast safety database that had been accumulated to that time, the sponsor proposed a stratification of safety data to pool studies of comparable completeness and reliability. A meeting was held on May 21, 1990, to consider the sponsor's proposal. A pre-NDA meeting occurred on May 4, 1991, during which stratification of safety studies into 3 levels was detailed and presentation formats were further delineated.

NDA #20,243 for the use of fluvoxamine in OCD was received on December 30 1991; the initial submission presented all data available as of December 31, 1990. A determination to file this NDA was made on February 18, 1992.

2.4 Directions for Use

The following recommendations are proposed by the sponsor:

Initial therapy should consist of fluvoxamine 50mg qHS for 4 days, then 100mg qHS for another 4 days. Subsequent doses should be titrated by 50mg increments, with 3-4 days at each dose level until maximum therapeutic effect is attained. The recommended daily dosage range is 100-300mg. Tablets should be swallowed with water and without chewing. Total daily doses of greater than 100mg should be taken in two equally divided doses. If unequal doses are taken, the larger dose should be taken at bedtime. Recommended duration of therapy for OCD is unclear. It is reasonable to consider continued treatment for a responding patient with periodic assessment of drug usefulness.

Since fluvoxamine is extensively metabolized by the liver, this being the major route of excretion, it will be important to consider recommendations for use in patients with hepatic impairment. Likewise, specific directions for use in the elderly may be warranted given decrements in hepatic and renal function with age.

Particular attention should be paid to drug-drug interactions which may need to be mentioned as contraindications or warnings in labeling, such as the contraindicated use of concurrent MAOI therapy with other SSRI's.

Finally, the potential for hepatotoxicity must be assessed to formulate any recommendation for monitoring liver function during therapy.

2.5 Foreign Marketing

Fluvoxamine was first approved for marketing in Switzerland in 1983 and has since been approved in 40 other foreign countries for the treatment of depressive disorders; the estimated worldwide exposure as of early 1993 is about million patients. There have been no foreign marketing withdrawals to date. Below are the 36 countries where fluvoxamine is marketed (as of May 1993).

EXHIBIT 4

PRESCRIBING INFORMATION

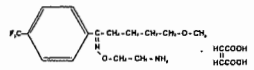
LUVOX™
fluvoxamine maleate

3E1252 Rev 1/95

DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$. Its molecular weight is 434.4.

The structural formula is:



Fluvoxamine maleate is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

LUVOX™ (fluvoxamine maleate) Tablets are available in 50 mg and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch, silicon dioxide, sodium stearyl fumarate, starch, synthetic iron oxides, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in Obsessive Compulsive Disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

Pharmacokinetics

Bioavailability: The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food.

In a dose proportionality study involving fluvoxamine maleate at 100, 200 and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283 and 546 ng/mL, respectively. Thus, fluvoxamine had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

Distribution/Protein Binding: The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL.

Metabolism: Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (See PRECAUTIONS - Drug Interactions)

Elimination: Following a ^{14}C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.

Elderly Subjects: In a study of LUVOX Tablets at 50 and 100 mg comparing elderly (aged 66-73) and young subjects (aged 19-35), mean maximum plasma concentrations in the elderly were 40% higher. The multiple dose elimination half-life of fluvoxamine was 17.4 and 25.9 hours in the elderly compared to 13.6 and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively.

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, LUVOX Tablets should be slowly titrated during initiation of therapy.

Hepatic and Renal Disease: A cross study comparison (healthy subjects vs. patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg bid, N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients. (See PRECAUTIONS - *Use in Patients with Concomitant Illness*)

Clinical Trials

The effectiveness of LUVOX Tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score of 23. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the Y-BOCS total score, compared to a 2 unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impressions (CGI) scale for both studies combined.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN POOL OF TWO OCD STUDIES

Outcome Classification	Fluvoxamine (N = 120)	Placebo (N = 134)
Worse	4%	6%
No Change	31%	51%
Minimally Improved	22%	32%
Much Improved	30%	10%
Very Much Improved	13%	2%

Exploratory analyses for age and gender effects on outcomes did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

LUVOX Tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX Tablets was established in two 10-week trials with obsessive compulsive outpatients with the diagnosis of Obsessive Compulsive Disorder as defined in DSM-III-R. (See Clinical Trials under CLINICAL PHARMACOLOGY.)

Obsessive Compulsive Disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of LUVOX Tablets for long-term use, i.e., for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use LUVOX Tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. (See DOSAGE AND ADMINISTRATION)

CONTRAINDICATIONS

Co-administration of terfenadine or astemizole with LUVOX Tablets is contraindicated (see WARNINGS and PRECAUTIONS).

LUVOX Tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that LUVOX Tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. After stopping LUVOX Tablets, at least 2 weeks should be allowed before starting a MAOI.

Potential Terfenadine and Astemizole Interactions: **Terfenadine and astemizole are both metabolized by the cytochrome P450IIIA4 isozyme, and**

it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of terfenadine and astemizole, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine and astemizole cause QT prolongation and torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted above, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the IIIA4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine or astemizole (see CONTRAINDICATIONS and PRECAUTIONS).

Other Potentially Important Drug Interactions
(Also see PRECAUTIONS - Drug Interactions)

Benzodiazepines: Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.
Alprazolam - When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, $T_{1/2}$.) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX™ (fluvoxamine maleate) Tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX Tablets.

Diazepam — The co-administration of LUVOX Tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration.

Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam is derived from a study in which healthy volunteers taking 150 mg/day of fluvoxamine were administered a single oral dose of 10 mg of diazepam. In these subjects (N=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level that was too low to measure over the course of the 2 week long study.

It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

Theophylline: The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately 3-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX Tablets.

Warfarin: When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX Tablets.

PRECAUTIONS
General
Activation of Mania/Hypomania: During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX Tablets should be used cautiously in patients with a history of mania.

Seizures: During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. LUVOX Tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide: The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for LUVOX Tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Closely monitored clinical experience with LUVOX Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

LUVOX Tablets have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. LUVOX Tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe LUVOX Tablets:

Interference with Cognitive or Motor Performance: Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX Tablets therapy does not adversely affect their ability to engage in such activities.

Pregnancy: Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with LUVOX Tablets.

Nursing: Patients receiving LUVOX Tablets should be advised to notify their physicians if they are breast feeding an infant. (See PRECAUTIONS - Nursing Mothers)

Concomitant Medication: Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX Tablets.

Alcohol: As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX Tablets.

Allergic Reactions: Patients should be advised to notify their physicians if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX Tablets.

Laboratory Tests
There are no specific laboratory tests recommended.

Drug Interactions
Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isozymes: Multiple hepatic cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also WARNINGS for details) and limited *in vitro* data for the IIIA4 isozyme, it appears that fluvoxamine inhibits the following isozymes that are known to be involved in the metabolism of the listed drugs:

IA2	IIC9	IIIA4
Warfarin	Warfarin	Alprazolam
Theophylline		
Propranolol		

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of the IID6 isozyme.

None of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine. However, the metabolism of fluvoxamine has not been fully characterized and the effects of potent inhibitors of IID6, such as quinidine, or of IIIA4 such as ketoconazole, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine or astemizole, warfarin, theophylline, certain benzodiazepines and phenytoin. If LUVOX Tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (See WARNINGS).

CNS Active Drugs:
Monoamine Oxidase Inhibitors: See WARNINGS

Alprazolam: See WARNINGS

Diazepam: See WARNINGS

Lorazepam: A study of multiple doses of fluvoxamine maleate (50 mg bid) in healthy male volunteers (N=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Lithium: As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of fluvoxamine maleate and lithium.

Tryptophan: Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of fluvoxamine maleate and tryptophan.

Clozapine: Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

Alcohol: Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Tricyclic Antidepressants (TCAs): Significantly increased plasma TCA levels have been reported with the co-administration of fluvoxamine maleate and amitriptyline, clomipramine or imipramine. Caution is indicated with the co-administration of LUVOX™ (fluvoxamine maleate) Tablets and TCAs.

Carbamazepine: Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of fluvoxamine maleate and carbamazepine.

Methadone: Significantly increased methadone (plasma level:dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Other Drugs:
Theophylline: See WARNINGS

Propranolol and Other Beta-Blockers: Co-administration of fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean five-fold increase (range 2 to 17) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of fluvoxamine and metoprolol.

If propranolol or metoprolol is co-administered with LUVOX Tablets, a reduction in the initial beta-blocker dose and more cautious dose titration is recommended. No dosage adjustment is required for LUVOX Tablets.

Co-administration of fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (N=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

Warfarin: See WARNINGS

Digoxin: Administration of fluvoxamine maleate 100 mg daily for 18 days (N=8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem: Bradycardia has been reported with the co-administration of fluvoxamine maleate and diltiazem.

Effects of Smoking on Fluvoxamine Metabolism: Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

Electroconvulsive Therapy (ECT): There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine maleate.
There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m² basis.

Mutagenesis: No evidence of mutagenic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility: In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate, (approximately 2 times the maximum human daily dose on a mg/m² basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

Pregnancy
Teratogenic Effects - Pregnancy Category C: In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m² basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m² basis.) While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of fluvoxamine on labor and delivery in humans is unknown.

Nursing Mothers
As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of LUVOX Tablets therapy to the mother.

Pediatric Use
Safety and effectiveness of LUVOX Tablets in individuals below 18 years of age have not been established.

Geriatric Use
Approximately 230 patients participating in controlled premarketing studies with LUVOX Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see Pharmacokinetics under CLINICAL PHARMACOLOGY), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS
Associated with Discontinuation of Treatment
Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Table 1: ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN OCD AND DEPRESSION POPULATIONS

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS FLUVOXAMINE	PLACEBO
BODY AS A WHOLE		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0%
DIGESTIVE		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
NERVOUS SYSTEM		
Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry Mouth	1%	<1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials:
LUVOX™ (fluvoxamine maleate) Tablets have been studied in controlled trials of OCD (N=320) and depression (N=1350). In general, adverse event rates were similar in the two data sets. The most commonly observed adverse events associated with the use of LUVOX Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 2 were: *somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating.* In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: *dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis and taste perversion.*

Adverse Events Occurring at an Incidence of 1%: Table 2 enumerates adverse events that occurred at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with LUVOX Tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Table 2: TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN OCD AND DEPRESSION POPULATIONS COMBINED[1]

	Percentage of Patients Reporting Event	
BODY SYSTEM/ ADVERSE EVENT	**FLUVOXAMINE N = 892**	**PLACEBO N = 778**
BODY AS WHOLE		
Headache	22	20
Asthenia	14	6
Flu Syndrome	3	2
Chills	2	1
CARDIOVASCULAR		
Palpitations	3	2
DIGESTIVE SYSTEM		
Nausea	40	14
Diarrhea	11	7
Constipation	10	8
Dyspepsia	10	5
Anorexia	6	2
Vomiting	5	2
Flatulence	4	3
Tooth Disorder[2]	3	1
Dysphagia	2	1
NERVOUS SYSTEM		
Somnolence	22	8
Insomnia	21	10
Dry Mouth	14	10
Nervousness	12	5
Dizziness	11	6
Tremor	5	1
Anxiety	5	3
Vasodilatation[3]	3	1
Hypertonia	2	1
Agitation	2	1
Decreased Libido	2	1
Depression	2	1
CNS Stimulation	2	1
RESPIRATORY SYSTEM		
Upper Respiratory Infection	9	5
Dyspnea	2	1
Yawn	2	0
SKIN		
Sweating	7	3
SPECIAL SENSES		
Taste Perversion	3	1
Amblyopia[4]	3	2
UROGENITAL		
Abnormal Ejaculation[5,6]	8	1
Urinary Frequency	3	2
Impotence[6]	2	1
Anorgasmia	2	0
Urinary Retention	1	0

[1] Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increase, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst and tinnitus.
[2] Includes "toothache," "tooth extraction and abscess," and "caries."
[3] Mostly feeling warm, hot, or flushed.
[4] Mostly "blurred vision."
[5] Mostly "delayed ejaculation."
[6] Incidence based on number of male patients.

Adverse Events in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference) in Rate from the Pooled Event Rates in OCD and Depression Placebo Controlled Studies: The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia and urinary retention.* These events are listed in order of decreasing rates in the OCD trials.

Vital Sign Changes
Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes
Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes
Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

Other Events Observed During the Premarketing Evaluation of LUVOX Tablets
During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories.

In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less than 1/1000 patients.

Body as a Whole: *Frequent:* accidental injury, malaise; *Infrequent:* allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; *Rare:* cyst, pelvic pain, sudden death.

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Cardiovascular System: *Frequent*: hypertension, hypotension, syncope, tachycardia; *Infrequent*: angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; *Rare:* AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

Digestive System: *Frequent*: elevated liver transaminases; *Infrequent*: colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, gingivitis, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; *Rare*: biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice.

Endocrine System: *Infrequent:* hypothyroidism; *Rare:* goiter.

Hemic and Lymphatic Systems: *Infrequent*: anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare*: leukopenia, purpura.

Metabolic and Nutritional Systems: *Frequent:* edema, weight gain, weight loss; *Infrequent*: dehydration, hypercholesterolemia; *Rare:* diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.

Musculoskeletal System: *Infrequent*: arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; *Rare*: arthrosis, myopathy, pathological fracture.

Nervous System: *Frequent*: amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; *Infrequent*: agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; *Rare:* akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

Respiratory System: *Frequent*: cough increased, sinusitis; *Infrequent*: asthma, bronchitis, epistaxis, hoarseness, hyperventilation; *Rare*: apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.

Skin: *Infrequent*: acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria.

Special Senses: *Infrequent*: accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; *Rare*: corneal ulcer, retinal detachment.

Urogenital System: *Infrequent*: anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[1], hematuria, menopause[1], menorrhagia[1], metrorrhagia[1], nocturia, polyuria, premenstrual syndrome[1], urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; *Rare*: kidney calculus, hematospermia[2], oliguria.
[1]Based on the number of females.
[2]Based on the number of males.

Non-US Postmarketing Reports
Voluntary reports of adverse events in patients taking LUVOX™ (fluvoxamine maleate) Tablets that have been received since market introduction and are of unknown causal relationship to LUVOX Tablets use include: toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, neuropathy, aplastic anemia, anaphylactic reaction, hyponatremia, acute renal failure, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
LUVOX Tablets are not controlled substances.

Physical and Psychological Dependence
The potential for abuse, tolerance and physical dependence with fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX Tablets were not systematically evaluated in controlled clinical trials. LUVOX Tablets were not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience
Worldwide exposure to fluvoxamine maleate includes over 37,000 patients treated in clinical trials and an estimated exposure of 4,500,000 patients treated during foreign marketing experience (circa 1992). Of the 354 cases of deliberate or accidental overdose involving fluvoxamine maleate reported from this population, there were 19 deaths. Of the 19 deaths, 2 were in patients taking fluvoxamine maleate alone and the remaining 17 were in patients taking fluvoxamine maleate along with other drugs. In the remaining 335 patients, 309 had complete recovery after gastric lavage or symptomatic treatment. One patient had persistent mydriasis after the event, and a second patient had a bowel infarction requiring a hemicolectomy. In the remaining 24 patients the outcome was unknown. The highest reported overdose of fluvoxamine maleate involved a non-lethal ingestion of 10,000 mg (equivalent of 1-3 months' dosage). The patient fully recovered with no sequelae.

Commonly observed adverse events associated with fluvoxamine maleate overdose included drowsiness, vomiting, diarrhea, and dizziness. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or mixed drugs) included coma, tachycardia, bradycardia, hypotension, ECG abnormalities, liver function abnormalities, convulsions, and symptoms such as aspiration pneumonitis, respiratory difficulties or hypokalemia that may occur secondary to loss of consciousness or vomiting.

Management of Overdose
1. An unobstructed airway should be established with maintenance of respiration as required. Vital signs and ECG should be monitored.
2. Administration of activated charcoal may be as effective as emesis or lavage and should be considered in treating overdose. Since absorption with overdose may be delayed, measures to minimize absorption may be necessary for up to 24 hours post-ingestion.
3. Maintain close observation as clinically indicated.
4. There are no specific antidotes for LUVOX Tablets.
5. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdosage.
6. Dialysis is not believed to be beneficial.

DOSAGE AND ADMINISTRATION

The recommended starting dose for LUVOX Tablets is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX Tablets in OCD, patients were titrated within a dose range of 100 to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

Dosage for Elderly or Hepatically Impaired Patients
Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

Maintenance/Continuation Extended Treatment
Although the efficacy of LUVOX Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Tablets 50 mg: scored, yellow, elliptical, film-coated (debossed "SOLVAY" and "4205" on one side and scored on the other)
Bottles of 100 ..... NDC 0032-4205-01
Bottles of 1000 ..... NDC 0032-4205-10
Unit dose pack of 100 ..... NDC 0032-4205-11
Tablets 100 mg: scored, beige, elliptical, film-coated (debossed "SOLVAY" and "4210" on one side and scored on the other)
Bottles of 100 ..... NDC 0032-4210-01
Bottles of 1000 ..... NDC 0032-4210-10
Unit dose pack of 100 ..... NDC 0032-4210-11

LUVOX Tablets should be protected from high humidity and stored at controlled room temperature, 15°-30° C (59°-86° F).

Dispense in tight containers.

CAUTION: Federal law prohibits dispensing without prescription.

SOLVAY PHARMACEUTICALS
MARIETTA, GA 30062

3E1252 Rev 1/95

KD00936

EXHIBIT 5

PROMOTIONAL MATERIALS
REQUEST FOR APPROVAL

MAP ITEM: (YES) / NO

Please review the attached material, make the necessary changes (please initial your changes), sign and date this cover sheet, and **return to Pat Silva**, Marketing Department, as quickly as possible. Thank you.

Date: 1/26/96 **DEADLINE:** 2/2/96

Re: LUVOX - OCD Compendium for Primary Care – Field Sales Force Use

Group Product Mgr: Jack Redmond	Signature: J Redmond	Date In: Date Out: 1/29/96	☐ Approved ☑ Approved with Changes ☐ Not Approved
Asst. Product Mgr: Sue Curro / Andrew Shales	Signature:	Date In: Date Out: 1/29	☐ Approved ☐ Approved with Changes ☐ Not Approved
VP Marketing: Kathleen Milligan	Signature: Kathleen Milligan	Date In: 2/7 Date Out: 2/9	☑ Approved ☐ Approved with Changes ☐ Not Approved
Sales Training: Kristin Hicks	Signature: Kristin Hicks	Date In: 1/30 Date Out: 2/15/96	☐ Approved ☑ Approved with Changes ☐ Not Approved
Medical Services: Dr. E. Demestihas	Signature:	Date In: 2/9 Date Out: 2/12	☐ Approved ☑ Approved with Changes ☐ Not Approved
Regulatory Affairs: Flo Gilson	Signature: F. Gilson	Date In: ~~2/10~~ 2/13/96 Date Out: 2/15/96	☐ Approved ☑ Approved with Changes ☐ Not Approved
Legal Counsel: Vicki Harrison	Signature:	Date In: Date Out:	☐ Approved ☐ Approved with Changes ☐ Not Approved
Additional:	Signature:	Date In: Date Out:	☐ Approved ☐ Approved with Changes ☐ Not Approved

Comments: This was the final wave of our direct mail campaign last year and we received numerous requests for more copies from both sales forces. This piece reinforces our "anxiety" story in the primary care store

NOTE: **After all changes have been made, the clean, reprinted final version MUST BE SUBMITTED to Regulatory Affairs for final approval.**

FINAL APPROVAL - Date: _____ **Approved by:** _____

M:\WP\COMM\SIGNATURE.DOC REV 1/96

Diagnosing the Patient with Obsessions and Compulsions

A COMPENDIUM OF DIAGNOSTIC CUES

NEW LOGOS
SOLVAY PHARMACEUTICALS
Upjohn THE UPJOHN COMPANY
P.O. Drawer 4650 · Clearwater, Florida 34698-9896

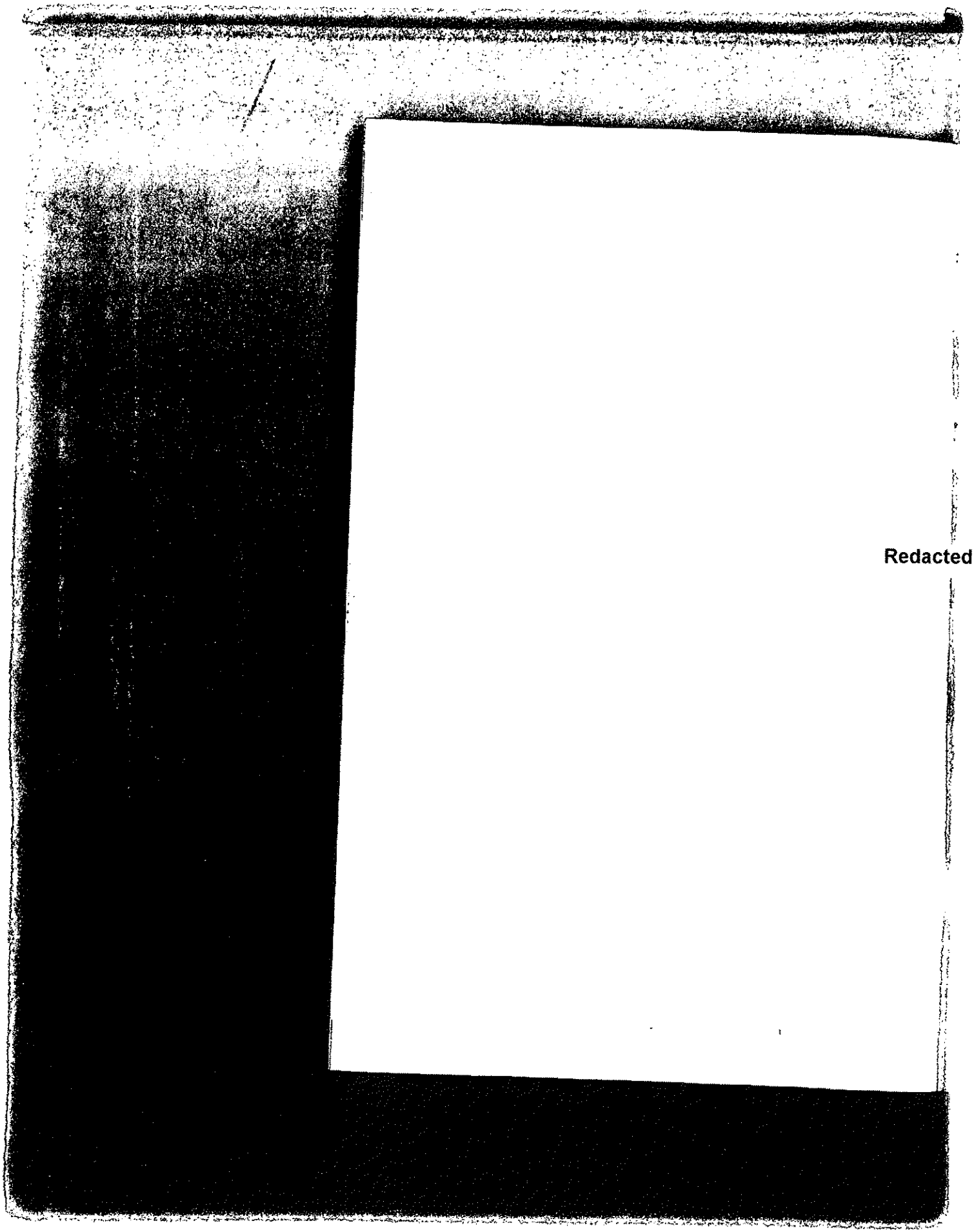
999188
USX

This compendium offers a compilation of diagnostic cues physicians have found useful in screening patients for obsessions and compulsions which may present in many manifestations.

The compendium is presented as a service to physicians by SOLVAY PHARMACEUTICALS, INC. and ~~THE UPJOHN COMPANY~~ UPJOHN COMPANY

Thanks and appreciation to the following physicians in both primary care and psychiatry who thoughtfully provided the information now being shared with colleagues nationwide.

Redacted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SCREENING FOR OBSESSIONS AND COMPULSIONS

THREE BASIC QUESTIONS

1. Do you have thoughts that bother you or make you anxious that you can't get rid of regardless of how hard you try?

2. Do you have a tendency to keep things extremely clean and to wash your hands very frequently, more so than other people you know?

3. Do you check things over and over to excess?

Change to these questions

2. Are there things you need to do to make the thoughts or anxiety go away that take alot of time such as washing, cleaning, checking, or arranging things ?

3. When you do these things one day, do you have to do them all over again the next day because the thoughts or anxiety come back?

ANXIOUS SYMPTOMS

Do you anticipate harm to an excessive degree?

Are you aware that your repetitious thoughts and acts are not realistic and are likely anxiety related?

Are you troubled by how to act on certain thoughts - like stepping over cracks on the floor, separation between tiles, etc.?

Are you superstitious?

Do you ever have any physical or mental routines that seem a bit unusual but at the same time relieve you?

Do you have any thoughts repeatedly that you think are strange?

Do these thoughts ever seem embarrassing, frightening or upsetting?

Do you get urges to do things?

Do you get upset when things are not just right?

Do you worry about your performance not being up to your standards in tasks coming up in the future?

When you worry about something, is it hard to let things (thoughts) go?

Do you worry about losing control?

ANXIOUS SYMPTOMS

Do you have a tendency to worry about things that may seem insignificant, trivial or strange?

Do you experience thoughts that are distressing?

Do you ever get angry at yourself for doing things you know other people would find ridiculous?

Are you uncomfortable when things aren't done exactly your way?

How do you feel if your routine is disrupted?

Are you ever anxious?

When anxious, do you need to do anything in particular, i.e., wash, clean, check, arrange or engage in thought rituals?

Do you worry a lot more than most?

Do you have trouble sleeping because of what happened today or what might happen tomorrow?

Do you become upset when changes occur in your routine or when furniture or objects are moved without your knowledge or permission?

Have you felt embarrassed about discussing your symptoms with others?

OBSESSIVE SYMPTOMS

Do you not do things because you obsess about it before and after?

Do you have difficulty making decisions?

Are there any thoughts (behaviors) that interfere with your concentration or effectiveness at work or at school?

Once a thought or memory comes into your mind - do you continue to think about it to the point where you can't accomplish things you want to do?

Do you worry about germs or becoming ill unnecessarily? Do people say you are a hypochondriac?

Do you have songs, words or phrases that repeat in your mind and you can't stop them?

What thoughts or activities interfere with you functioning normally or the way you want to function each day?

What bothers you the most?

Do you worry to the point where it interferes with your eating, sleeping, or recreational time?

Are you a cautious person? Do you have to check over your work repeatedly to ensure that you haven't made a mistake, or do you need to check repeatedly to ensure that doors are locked, the coffee pot is unplugged or that you have turned off the curling iron?

Are time commitments a problem to honor?

Do you feel something is wrong with your body which your doctor cannot confirm?

Do you think that you worry more than most people do?

OBSESSIVE SYMPTOMS

Do you worry that something terrible is about to happen to you or a loved one?

Can you go to sleep if there are dirty dishes in the sink?

Do you fear that you are abnormal or crazy?

Do you find it very difficult to leave a thought before you have finished thinking it through?

Do you worry excessively about hurting others by your words or deeds?

Is there any family member that is an over-worker or very attentive to details?

Do you become irritable if others fail to "cooperate" with your rituals?

Do you have repetitive morbid thoughts, such as someone will die, especially if you do or don't do a certain thing?

Do you get upset when people disturb things at your house, then have the need to rearrange them as quickly as you notice them?

Are there certain sounds which you can't get out of your head once you hear them?

Do you find yourself doing things like going shopping and not getting out of the car, or wanting to go shopping but can't decide on the exact right item, even though your sizes and color choices are there?

Are you bothered by things not being in order?

Do you have any recurrent thoughts that don't make much sense that bother you?

OBSESSIVE SYMPTOMS

Do you have thoughts that keep coming into your mind that you can't get rid of?

Are numbers special to you?

How much do you worry about cleanliness?

Do you have a hard time leaving your house for fear of forgetting to turn something off?

Do you believe in lucky colors, numbers, or animals?

Is it important for you to have things balance or be symmetrical?

Are you very particular about the way things are done?

Do you feel compelled to do things in exactly the same way?

Do you remind family members several times of the same things to do?

Do you worry excessively about harming others through negligence or carelessness?

Do you constantly find yourself early to work and meetings? Are you always the first to show up?

Are you always the last to leave work, often even cleaning up after others?

Do you run ideas over and over in your mind that may not be important to the issues at hand?

Do you worry constantly about your appearance and have to constantly ask those around you for reassurance that you look alright, that you are attractive enough?

Do you sleep all night? How do you feel in the morning?

OBSESSIVE SYMPTOMS

Are you set in your ways?

Do you worry excessively about the safety of your loved ones?

Do you get caught up in details?

Do you feel pressure to use every minute productively?

Is there someone that you can't stop thinking about, even if it gets you in trouble?

Do you feel that unless you personally handle a task it isn't done correctly?

Do you have a tendency to not want to touch objects for fear of contamination?

If someone spills crumbs on the floor and leaves them, how does it make you feel?

What thoughts do you have that seem to recur frequently even when you attempt to stop thinking the idea? How much does it bother you when that happens?

Do you have forbidden thoughts about sex?

Do you lose sleep at night worrying about things you may have done or not done?

Do you recognize your obsession but feel powerless to control it?

Do you have any unusual or recurrent religious thoughts?

Do you doubt everything?

COMPULSIVE SYMPTOMS

Do you check and recheck door locks or stoves before going to bed or leaving home?

Do you start picking up things upon entering your home and putting them in place before doing anything else?

Describe how you clean a bathroom.

Do you make an extensive checklist to follow each day?

Are you able to attend to your work at your desk if everything on (and in) the desk is not in perfect order?

Do you do certain things to prevent something bad from happening to yourself or a family member that you know are irrational?

How long do you spend taking a bath?

Do you try not to step on the lines on the sidewalk?

Do objects on a table have to be parallel and perpendicular?

Do the hangers in your closet have to be equidistant apart?

Does your family complain about your need for a clean house?

Do you save or hoard things you know are worthless?

Do you need to get up early to take care of rituals?

Are you late for things because you have to do something over and over?

Do you organize things (like clothing, food pantry) by color, shape or material?

Do you talk to yourself?

Does hanging and folding clothes take a lot of time?

COMPULSIVE SYMPTOMS

Do you find yourself slower than other people to get essential tasks done? Always late?

Do you find yourself using alcohol or drugs to turn off all thought?

Do you have a compelling urge to touch everything in the room?

Has anyone told you that you are too careful or that you clean too much?

If you touch something/someone, must you wash?

Do you do repetitive rituals with your body, such as blink eyelids, picking, smell part of your body, jerk head, or anything else, for no good reason and find it hard to stop?

Do you count things in a room, such as tiles, books, etc., for no purpose?

Do you have rituals or behaviors you do everyday which interfere with your ability to get to places on time?

Do you wash hands excessively just because you feel contaminated?

Are there things that you need to do in order to make the thoughts or anxiety go away?

Do you wash your hands more than 10 times a day?

Do you keep a lot of lists?

When you wash or bathe, do you have to wash your body parts in a sequential, ritualistic way?

Do you find yourself caught up doing something time and time again so that you miss out on something important?

Do you need to have things in a certain place or order?

Do you procrastinate and get stuck?

COMPULSIVE SYMPTOMS

Do you frequently return home in the morning to make sure that you locked the doors?

Do you have to rewash the dishes or remake the beds after others do this?

Do you need to get up early to take care of rituals?

Have you been to a dermatologist for treatment of your hands but never told him you wash unusually frequently?

Do you and your spouse quarrel a lot over neatness in the house?

Do you straighten/pick-up your house in order to relax?

Do you tend to adjust things - such as items on a table?

Are you extra careful to keep the place (home or work) tidy or clean?

Do you wear out your vacuum cleaner every year?

Could you leave a task unfinished to do an enjoyable activity?

Is there anything that you do that you feel is illogical yet you still do over and over?

Do you spend a lot of time keeping things arranged just so?

Do you have any habits that you have tried to break - but it's just been too difficult?

Do you clean things that are already clean or count things that don't need to be counted?

Do you refold laundry if it's "different"?

What happens if your routine is upset? Must you start again?

SYMPTOMS OF OBSESSIVE COMPULSIVE DISORDER

COMMON OBSESSIVE, INTRUSIVE THOUGHTS	
FEAR OF CONTAMINATION	Fearing dirt, germs, cancer, AIDS, bodily wastes, asbestos, chemicals, radiation, sticky substances
FEAR OF CAUSING HARM TO ANOTHER	Putting poison in food, spreading illness, smothering a child, pushing a stranger in front of a car, running over a pedestrian
FEAR OF MAKING A MISTAKE	Setting fire to the house, flooding the house, losing something valuable, bankrupting the company
FEAR OF BEHAVING IN A SOCIALLY UNACCEPTABLE MANNER	Swearing, making sexual advances, saying the wrong thing
COMMON COMPULSIVE, RITUALISTIC BEHAVIORS	
CHECKING	Repeatedly checking to see if light switches, appliances and faucets are off; or doors locked
COUNTING/REPEATING	Counting to a certain number or counting objects over and over; repeatedly performing a behavior before being able to move on
COLLECTING/HOARDING	Collecting old objects, mail, trash to the point of filling up one's home
CLEANING/WASHING	Hand washing, showering or cleaning oneself repeatedly
ARRANGING/ORGANIZING	Arranging items in perfect symmetry or in a certain order (for example, cans or books on shelves)

EXHIBIT 6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC

TRANSMITTED VIA FACSIMILE

Ms. Florence S. Gilson
Manager, R&D Compliance
Solvay Pharmaceuticals
901 Sawyer Road
Marietta, GA 30062

Re: NDA 20-243
Luvox (fluvoxamine maleate) Tablets
MACMIS File ID # 2405

Dear Ms. Gilson:

This letter is in response to Solvay Pharmaceuticals' (Solvay) August 25, 1994, request for the Division of Drug Advertising, Marketing, and Communications (DDMAC) to review the draft launch promotional materials for Luvox (fluvoxamine maleate) Tablets. These comments are subject to change pending final approved labeling.

The sales aid will be used as a guidance document for the majority of our comments. Since many claims and presentations in these materials are similar or closely related, the comments on a particular claim or presentation apply to all such claims and presentations whether they appear now or in the future. We offer the following comments:

Page 3

1. "Primary OCD often coexists with depression and/or anxious conditions, such as phobias or panic disorder."

Use of the word, "primary," in this context suggests that comorbid disorders are of secondary importance to OCD. This suggestion is misleading, therefore the word, "primary," should be deleted.

2. "OCD patients frequently present with coexistent disorders" chart.

This chart describes the percent of patients with obsessive compulsive disorder (OCD) that will also suffer a coexistent disorder during their lifetime. Coexistent disorders include

major depressive disorder, simple phobia, separation anxiety disorder, social phobia, eating disorder, alcohol abuse, panic disorder, and Tourette's syndrome. Therefore, this chart implies that Luvox will be effective in treating OCD patients with these coexistent disorders.

The exclusion criteria for the two pivotal studies supporting Luvox's efficacy in treating OCD included the following:

1. Met DSM-II-R criteria for a major affective disorder, had a pre-study HAMD total score ≥20, or a HAMD item 1 score >2.

2. A history of other psychiatric disorders including schizophrenia, psychotic symptoms, bipolar affective disorder, organic dementia, psychosurgery, personality disorders which might interfere with compliance, Tourette's syndrome, panic disorder, agoraphobia, and eating disorders not secondary to OCD, or substance abuse or alcoholism, within the prior year.

The pivotal studies systematically excluded OCD patients with the coexistent disorders described in the chart. Therefore, all presentations of this chart or presentations of the information in the chart should be accompanied by a prominent disclosure that Luvox has not been studied in patients with these coexisting disorders.

3. "It is estimated that only 6% of OCD sufferers currently receive treatment."

This statistic for the number of untreated OCD sufferers is based upon IMS diagnosis data and the National Institute of Mental Health's (NIMH) estimate of the prevalence of OCD. However, this point estimate fails to account for the uncertainty in the supporting data. Because both IMS data and the NIMH data are known to have a wide margin of error, it is extremely unlikely that the 6% estimate is accurate. Additionally, the IMS diagnosis data estimates the number of patients who were diagnosed with OCD, not the number of patients who receive treatment for OCD. Therefore, the standard deviation surrounding the 6% estimate should be included in all claims concerning undiagnosed OCD sufferers. Alternatively, this statistic could be replaced with a less specific claim such as, "Few OCD sufferers are currently diagnosed."

Page 4

4. "Introducing a highly selective serotonin reuptake inhibitor" graphic box

Luvox is a member of the class known as selective serotonin reuptake inhibitors (SSRIs). The adjective "highly" suggests a ranking of the members of the class and/or that Luvox represents an improvement in this class of drugs. Therefore, the word "highly" should be deleted from this claim.

5. Duration of use.

Presentations of efficacy data should be accompanied by the disclosure that the effectiveness of Luvox has not been established for long-term use, i.e., for more than 10 weeks.

6. Dosage key for "Proven effective in improving OCD symptoms" graph

The key for this graph states that the dosage range for Luvox therapy in this study was 50-300 mg/day. However, the target dose range for this study was 100-300 mg/day and the minimal allowable dose was 100 mg/day. Therefore, this description should be revised accordingly.

7. "In a separate 6- to 8-week trial, symptom improvement was seen as early as 2 weeks and continued throughout treatment," and

   "Symptom improvement may be seen as early as 2 weeks and continues throughout treatment" graph

Efficacy claims that are not described in the approved product labeling must be supported by substantial evidence, generally two adequate and well-controlled studies. The reference for this claim and graph is, "Efficacy of fluvoxamine in obsessive-compulsive disorder: a double-blind comparison with placebo," by Goodman, et al. If the Goodman, et al., study was adequate and well-controlled, substantial evidence would require an additional confirmatory study. However, the Goodman study does not appear to be adequate and well-controlled for reasons that include, but are not limited to:

(a) This study is not of adequate design to measure time-to-onset. The determination of time-to-onset was neither the primary nor secondary outcome measure of this study.

(b) The efficacy analysis of this study was based upon only those patients completing at least two weeks of treatment, as opposed to a more conservative intent-to-treat analysis. Therefore, this method of analysis may have biased the results in favor of Luvox.

(c) The finding that statistically significant decreases in total Y-BOCS score occurred at Week 2 does not appear to be corrected for multiple comparisons. Therefore, this statistical treatment may have biased the results in favor of Luvox.

Additionally, the Goodman study states that although a statistically significant decrease in Y-BOCS score was detected at Week 2, clinically meaningful improvement was not demonstrated until after 6 weeks of treatment. Therefore, the claim that symptom improvement may be seen as early as two weeks would misrepresent the findings of the authors.

Moreover, in the two pivotal studies' "observed cases" data sets, the Y-BOCS and NIMH-OCS scores over time did not show a statistically significantly difference between Luvox and placebo by Week 2.

For the above reasons, this claim, graph, and all other representations of time-to-onset based upon the Goodman study should be deleted.

Page 5

8. "Both Luvox and Anafranil were effective in controlling the symptoms of OCD in two randomized double-blind studies" graphs.

The two studies from which these graphs are derived, report number H.114.929/M and protocol 114.8.02 in Attachment V of the launch submission, were conducted without a placebo control. Placebo response rates are population-dependent and vary dramatically and unpredictably. Because this response rate can be so significant, the results of the placebo-control arm serve as a baseline to which the active drug therapy may be compared. Without the context of this baseline measure, it is impossible to know if patients would have improved without drug treatment. Therefore, the results of these studies are uninterpretable and inadequate to support this claim. Accordingly, efficacy claims and representations based upon these two studies should be deleted.

9. "Favorable pharmacokinetic profile" chart.

This chart describes select pharmacokinetic parameters of Luvox as they compares to Anafranil and Prozac. These parameters include presence of an active metabolite, half-life of parent compound and active metabolite(s), and time to steady-state plasma concentration. The presentation of these select comparative pharmacokinetic parameters suggests that differences in pharmacokinetics may be correlated with differences in clinical effects. For example, this presentation suggests that Luvox is a "faster-acting drug" than Anafranil or Prozac. However, this presentation fails to feature other seemingly unfavorable pharmacokinetic parameters, such as protein binding or linearity of pharmacokinetics. Therefore, this selective presentation of pharmacokinetic parameters is misleading. This chart should present a balanced picture of the pharmacokinetics of Luvox as they compare to Prozac and Anafranil. Alternatively, the pharmacokinetics of Anafranil and Prozac could be deleted from this presentation.

Additionally, the pharmacokinetic information for Prozac is not accurate. According to current labeling, the half-lives after chronic dosing for fluoxetine and norfluoxetine are 4-6 days and 4-16 days, respectively.

Finally, this chart lacks the information that in vitro activity does not necessarily imply clinical effect. This information should be presented with greater prominence and readability than the footnote on page 10.

10. "Luvox tablets are more selective for serotonin relative to norepinephrine and dopamine than Anafranil or Prozac."

As discussed in Comment 9, this claim suggests superiority of Luvox over Anafranil and Prozac. Therefore, this comparative presentation is misleading. The presentation of pharmacokinetic data describing Luvox would not be misleading.

Page 6

11. Graphic of woman.

The graphic on pages 1, 2, 4, 8 and 9 of the sales aid is a portrayal of a frowning woman with a teardrop on her right cheek. The woman on this page no longer has a teardrop on her cheek and is smiling. This change in the graphic suggests that Luvox will improve typical symptoms of depression, such as sadness and despair.

Additionally, this graphic, which appears only on the page that discusses the safety of Luvox, contains words such as, "safety," "minimal agitation," and, "tolerability." DDMAC recognizes that these adjectives could be describing a patient without the symptoms of OCD. However, they could also be describing the safety profile of Luvox. For both of these reasons, this graphic would be misleading, and should be revised.

12. "Targeted for excellent patient tolerability" headline.

This page presents information about the risks associated with Luvox therapy. Accordingly, the headline should cue the reader that risk information will follow. This headline does not alert the reader that risk information will be presented. Therefore, it should be revised to more accurately reflect the contents of the page.

Additionally, the claim, "excellent patient tolerability" would be misleading. Twenty-two percent of the 1,087 patients in the clinical trials in North America discontinued treatment due to an adverse event. The most common drug-related adverse events associated with discontinuation were nausea, somnolence, insomnia, nervousness and headache. Therefore, it is inaccurate to describe the tolerability of Luvox as "excellent."

13. "Low incidence of agitation."

The word "low" is ambiguous in this context. Therefore, the specific incidence of occurrence of agitation for both Luvox and placebo should be added to this claim.

14. "Low level of anticholinergic activity.

This claim suggests that Luvox is not associated with the adverse events generally associated with drugs that inhibit cholinergic receptors. These adverse events generally include constipation, dizziness, and dry mouth. However, Luvox is also associated with these adverse events: constipation, 14.4%, dizziness, 9.4%, and dry mouth, 11.9%. Therefore, this claim would be misleading.

15. "No clinically significant changes in ECG or blood pressure."

Fair balance requires that this claim be accompanied by the disclosure that Luvox has not been studied in patients with a recent history of myocardial infarction or unstable heart disease. The presentation of this disclosure should be reasonably comparable to the efficacy claim.

16. "Wide margin of safety in overdose."

This claim minimizes the need for aggressive management in overdose situations. Therefore, we recommend this claim be balanced with:

(a) information about human experience with overdose as described in the approved product labeling; and

(b) the recommendation for prescribers to write the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose should be added to the promotional materials.

17. "Adverse events are generally mild and transient."

As discussed in Comment 5, it is inaccurate to describe the adverse events associated with Luvox as "mild and transient."

18. "The most common adverse events in patients taking Luvox Tablets for OCD in placebo-controlled trials were those typical of SSRIs: insomnia, nausea, somnolence, and asthenia."

We are concerned with two aspects of this statement. First, the phrase, "were those typical of SSRIs," minimizes the importance of the risk information. Therefore, this phrase should be deleted.

Second, this claim should include the most common adverse events associated with both drug therapy and placebo. We recommend listing the drug and placebo rates for the following events: insomnia, somnolence, nausea, asthenia, abnormal ejaculation, nervousness, dry mouth, and constipation.

19. Potential terfenadine and astemizole interactions

This black box warning information should be added to the promotional materials. This information should be presented with a prominence and readability reasonably comparable to claims about drug efficacy.

20. Interference with cognitive and motor performance

The precaution about potential interference with cognitive and motor performance should be added to the promotional materials. This information should be presented with a prominence and readability reasonably comparable to claims about drug efficacy.

Page 7

21. "Worldwide experience in 36 countries and 4.5 million patients."

DDMAC recognizes that this information was excerpted from the approved product labeling. However, the labeling presents this information in the context of the incidence of overdose. When presented out of context, this claim suggests that this experience was gained in OCD patients. To the contrary, the majority of this experience was gained in patients with depression. Therefore, this claim is misleading.

This information should be presented in the context described in the labeling. Alternatively, the worldwide experience described in the claim could be limited to OCD patients.

22. "BID dosing recommended for over 100 mg/day."

This dosage information should be further clarified with the recommendation that, if the doses are not equal, the larger dose should be taken at bedtime.

23. "Targeted for obsessions and compulsions" tag line

This tag line suggests that Luvox acts solely on improving the obsessions and compulsions associated with OCD without causing any other effects, such as adverse events. Because Luvox is associated with adverse events, this tag line would be misleading.

Page 10

24. "Luvox tablets are more selective for serotonin relative to norepinephrine and dopamine than Anafranil or Prozac" and accompanying chart.

Please see Comment 9.

File Card

Page 5

25. "Rapid achievement of steady-state blood levels and a short half-life contribute to positive patient management."

This claim correlates the pharmacokinetic data describing steady-state blood levels and half-life with the clinical benefit of positive patient management. However, pharmacokinetic data alone

is not adequate to support this claim of clinical benefit. Therefore, this claim would be misleading.

Press Release

Paragraph 1

26. "Currently, an estimated 94 percent of people with OCD are not receiving medical treatment."

As discussed in Comment 3, this point estimate is likely inaccurate and should be revised according to the discussion in Comment 5.

Paragraph 2

27. "Luvox will offer advantages over traditional OCD drug therapy..."

This claim suggests that Luvox has several advantages over traditional OCD drug therapy. Please provide support for this claim in the form of adequate and well-controlled studies between Luvox and all other OCD therapies. In the absence of supporting data, this claim should be deleted.

28. "effectively reduce the symptoms of OCD with fewer side effects than a tricyclic antidepressant."

This claim suggests that Luvox has a superior safety profile compared to a tricyclic antidepressant. Superiority claims must be supported by substantial evidence, generally two adequate and well-controlled studies. The reference for this claim is, "Fluvoxamine: a multicentre, prospectively-randomized, double-blind, parallel group comparison with clomipramine in the treatment of obsessive compulsive disorder," by Ashford, et al. If the Ashford, et al., study was adequate and well-controlled, substantial evidence would require an additional confirmatory study. However, the Ashford, et al., study is not of adequate design to demonstrate such a difference. For example, this study fails to explore the full dose range of both comparators, account for the actual doses administered, or document the specific nature of the adverse events.

Additionally, this statement implies that the tricyclic antidepressant in question is Anafranil, since Anafranil is the only tricyclic antidepressant indicated for OCD. This implication would be misleading. For all of these reasons, this statement should be deleted.

Paragraph 3 and 11

29. "Luvox...been studied for numerous indications..."

    "Regulatory registrations are being sought for depression and other indications in several major countries."

This discussion suggests Luvox is potentially effective in treating numerous diseases in addition to OCD. Because Luvox has only one indication in the United States, these discussions are outside the scope of the approved product labeling. Therefore, these discussions should be deleted.

Paragraph 4

30. "Evidence shows that OCD is a biological illness involving an imbalance of the brain chemical serotonin, which sends impulses from one nerve cell to another."

Although there is evidence that suggests that this might be the mechanism of OCD, this theory has not yet been proven. Therefore, this statement should be revised to suggest that this theory is currently hypothetical.

Video News Release

31. Shot of Fran and Dr. Hollander in Office: "Studies have shown that 50 to 80 percent of patients who receive medication experience a reduction in obsessive thoughts and perform fewer rituals."

A reference is not provided for this statistic describing the percent of patients who are successfully treated. Therefore, DDMAC assumes that this statistic is the opinion of Dr. Hollander. Anecdotal experience is not adequate to support such a statistic. In the absence of other supporting data, this statistic should be deleted.

32. Script

Please provide the script for the entire video news release. This submission includes the script for only the first 2:24 minutes of the video.

33. Failure to provide fair balance.

The press release, audio news release, and video news release fail to include discussions of the major warnings, precautions and adverse events associated with Luvox therapy. Fair balance

requires such discussions to be presented in a manner reasonably comparable with claims about drug efficacy.

Since the layout copies are tentative these comments should be considered preliminary and are restricted to the layouts as submitted and do not imply pre-clearance of the final promotional materials. These comments may change based on the incorporation of DDMAC's recommendations into the final text. Also, factors such as variations in print size, layout, and color may affect our comments on the final materials.

Please address any questions or comments to the undersigned at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-240, Rm 17-B 20, 5600 Fishers Lane, Rockville, Maryland 20857.

In all future correspondence regarding this matter, please refer to the MACMIS File ID# 2405, in addition to the NDA number.

Sincerely,

Sherry Danese

Sherry Danese, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

EXHIBIT 7

Selling Luvox to Primary Care Physicians

Luvox

- First synthesized in 1971 in Switzerland
- Brought to market in 1983 in Europe
- The first SSRI
- Approved for OCD in the U.S. in 1995
- Used worldwide for depression, panic disorder, OCD, PTSD, autism, Tourette's, bulimia, BDD, pathologic gambling.....The OC Spectrum

Pharmacokinetics

- 16 hour half life - children, elderly, multiple medication patients
- 80% protein bound
- 7 days to steady state
- favorable interaction profile - CYP2D6
  beta blockers, codeine, anti arrhythmics, dextromethorphan, atypical antipsychotics, TCA's, loratadine.....polymorphism

Side Effects

- Nausea similar to other SSRI's
- Agitation\nervousness lower than with other SSRI's
- Sleep may be improved - melatonin effect
- Weight gain less than other SSRI's
- Sexual dysfunction lower than other SSRI's
- Some niche Luvox as their "2nd line drug" for patients with above problems

Safety

- Used in over 10 million patients worldwide
- Over 40,000 patients in clinical trials
- Phase IV studies ongoing in mixed anxiety\ depression, hypochondriasis, dysthymia, social phobia and geriatric depression
- P450 interaction profile
- No "surprises" due to length of time on the market

Good Luvox Candidates

- The elderly - heart, pain, benzo. users
- Patients who are anxious, nervous, agitated and\or who cannot sleep - taking benzo.
- Children - 1/2 life, erratic metabolizers
- Patients who you do not want to make sexually dysfunctional or who are having problems with their current medication
- Patients with weight gain issues

What will make Luvox attractive to Primary Care Physicians?

What are their problems?
What do they need?
Who is providing it?

What about Pharmacokinetics?

Half-life

- While this is a characteristic of Luvox, how do you position it to this group? Prozac has the longest 1/2 life and the largest % share. Do they *need* a short 1/2 life SSRI?

7 days to steady state

- This means that, at a fixed dose, a steady plasma level will be reached in 7 days. A fact, yes, but what *problem* does this solve?

Cont'd.

80% protein binding

- Luvox is moderately bound at this level. Other bound drugs can be displaced by SSRI's with higher percentages. No one agrees on any outcomes here. A *need*??

Food effect on absorption

- What actually happens if someone eats and takes Zoloft? With two billion in sales, I'm betting not much. Not a meaningful parameter. Again, a *need*?

Cont'd

Drug interactions

- This is the most confusing area of all for *any* doctor. The 3A4 pathway is the biggest concern because of cardiac problems. All SSRI's have 3A4 issues. The bottom line is: SSRI drug interactions do not kill people. Give your doctors this perspective and don't pursue this topic. Not a *need* unless told so.

Cont'd

Active metabolite

- It is a fact that we do not have one and that Prozac and Zoloft do. However, is there a relevant PC *outcome* in our favor with this fact? Not really.

Side Effects

Nausea

- The PI shows a higher % for Luvox than for the other SSRI's. This was in OCD dosing. Lower %'s have been shown in more recent head to heads. We don't win or lose here.

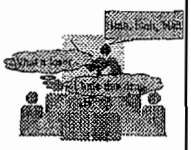
Weight Gain

- Information is anecdotal for all drugs. Reports are favorable for Luvox, but anyone can: 1) make a claim or 2) discredit your claim. Not a good proactive pursuit.

Cont'd

Sexual Dysfunction

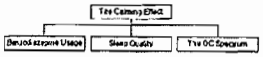
- Highly crowded area. We do look very good here and can present a solid case. However, as a single topic to pursue, we may get lost in the "noise" level.



Our biggest impact with Luvox will be with……..

Calming

The "Calming" Effect
3 Components to our sale:



I. The Benzodiazepines

- This class of drugs is used for anxiety - often called *anxiolytics*. They are very effective but are generally perceived as being addictive. There are few alternatives to benzos which work (Buspar). Patients often use them in excess of their RX and become problems for doctor and staff by calling or making appts. for the purpose of getting more. Headache! Controlled! DEA!

Benzos cont'd

Common Benzodiazepines

Xanax (alprazolam)
Ativan (lorazepam)
Klonopin (clonazepam)
Librium (chlordiazepoxide)
Valium (diazepam)
Serax (oxazepam)

OC Related Anxiety, perhaps with depression, is very common in our PCP offices

How do doctors handle these patients?

Usually with an SSRI and the "short term" addition of a benzo.

Prozac and a small amount of Xanax
Zoloft and a small amount of Klonopin
Paxil and a small amount of Ativan

The problem then becomes:

- How do I get them off?
- How do I handle them wanting more?*
- How do I decide who really needs it?
- How long is long enough?
- Am I doing the right thing each time I RX?
- The general sense that these drugs are bad, yet not having a good alternative.

* Ask a nurse or receptionist if this is a problem

So, we need to:

1. Ask about his benzo usage (length of time, problems, thoughts on using them, adjunctive use with an SSRI).

2. Inquire about this patient population. (specifically those on a SSRI + Benzo) ***KEY*** - Ask if these patients tend to worry or ruminate excessively, have other persistent thoughts, feel their thoughts are "out of control", etc....

3. Position Luvox, with it's low incidence of agitation, as a *single tablet, SSRI alternative* for this group.

4. Give him the method for getting patients off of an SSRI + Benzo and onto Luvox

The Bottom Line:

"Doctor, if you could achieve an effect with Luvox alone similar to that you achieve by adding a benzo to another SSRI, isn't that worth a try?"

- *By implementing this strategy, we are simply outlining a specific group, which we know to exist, as a target for our side effect advantage. This leads to.....*

How Do We Support our Claim?

- Rapaport. A Comparison of Fluvoxamine and Fluoxetine in the Treatment of Major Depression
- Kiev. A Double-Blind Comparison of Fluvoxamine and Paroxetine in the Treatment of Depressed Outpatients
- Laws. A multicentre double-blind comparative trial of fluvoxamine vs. lorazepam in mixed anxiety and depression

In each of the SSRI papers, point out that Luvox has a lower incidence of nervousness and agitation and an equal efficacy to Ativan - a benzodiazepine.

II. Sleep Quality

- Benzos are often Rx'd with SSRI's to help with loss of sleep - a common complaint.
- Melatonin is a natural hormone which promotes sleep.
- Melatonin levels increase at night.
- Luvox increases plasma levels of melatonin.
- Dosage time is key. See "Beyond Prozac"
- Use to supplement our position.

III. The OC Spectrum

- OCD is a "confining" diagnosis - thought to be just hand washing and checking - (2%)
- Many more disorders are now considered OC in nature and given new names - (see diagram). They all score high on Y-BOCS. Perhaps 10-15% of population or more.
- Point out hypochondriasis, compulsive eating, spending, gambling, social phobia.
- We want to mainstream Luvox in his mind

How To Make the Change

- Stop the current SSRI; wait one week
- Initiate Luvox 50 mg
- Hold at 50 mg for one week (with Benzo)
- Increase Luvox to 100 mg; hold one week
- Taper the benzo according to your protocol
- Counsel him to "sell" the patient that this is something they have not tried and that it will be effective. This "buy in" is crucial!!

Odds and Ends

- 100 mg *is* the target dose
- The 15 second call = "Doctor, you are signing for Luvox, the SSRI which may eliminate the need for you to Rx benzos"
- Talk of Luvox as an SSRI; avoid indication
- Give patients to get patients. Ex: lethargic, poor compliance, poor sexual performers, hypersomniacs. It doesn't hurt to state who you don't want along with who you do.